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HIGH LIGHT CME

Predictors of recurrent stroke in African Americans

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Abstract—*Background:* Stroke incidence and mortality are disproportionately higher among African Americans than among whites. *Objective:* To describe the recurrent stroke characteristics and determine the predictability of known vascular risk factors for stroke recurrence in African Americans. *Methods:* The authors followed 1,809 African Americans in the African-American Antiplatelet Stroke Prevention Study with recent noncardioembolic ischemic stroke for recurrent stroke, recurrent stroke subtype, and disability. *Results:* Of the subjects, 10.6% experienced a recurrent stroke during follow-up. The mean interval between eligibility and recurrent stroke was 325 days (median 287 days, SD = 224 days). Stroke recurrence resulted in an average 1.5-point increase in the National Institute of Health Stroke Scale ($p < 0.001$) and a 3.5-point decrease in modified Barthel Index ($p < 0.001$). Of previously nondisabled subjects, 48% became disabled or died after stroke recurrence ($p < 0.0001$). Longitudinal analysis resulted in a hazard for recurrent stroke for each 10-mm Hg increase in systolic blood pressure of 1.103 (95% CI: 1.031 to 1.179, $p = 0.004$), pulse pressure 1.123 (95% CI: 1.041 to 1.213, $p = 0.003$), and mean arterial pressure 1.123 (95% CI: 1.001 to 1.260, $p = 0.048$). Multivariate analysis revealed increases in the recurrent stroke hazard for increases in baseline Glasgow Outcome Score (1.449, 95% CI: 1.071 to 1.961, $p = 0.016$) and increases in longitudinal pulse pressure (1.009, 95% CI: 1.001 to 1.017, $p = 0.029$). *Conclusion:* Recurrent stroke leads to disability and disability predicts recurrent stroke. Hypertension is the most predictive modifiable stroke risk factor.

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Stroke incidence and mortality are generally disproportionately higher among African Americans than among whites.[1] A greater vascular risk factor burden in African Americans may account for part of this difference.[2] In addition, risk factor awareness, treatment, and control may be poor among African Americans including those surviving an ischemic stroke.[3] Our objective was to describe the recurrent stroke characteristics and determine the predictability of known vascular risk factors for stroke recurrence in the African-American Antiplatelet Stroke Prevention Study (AAASPS).

Methods. The AAASPS is a multicenter, randomized, double-blind, controlled, clinical trial comparing the effectiveness of aspirin 325 mg twice daily to ticlopidine hydrochloride 250 mg twice daily for preventing the composite primary outcome recurrent stroke, myocardial infarction, and vascular death. African American ischemic stroke patients were enrolled from 1995 to 2002 within 7 to 90 days (mean 45 days) of the eligibility stroke. Patients requiring carotid endarterectomy or whose eligibility stroke was deemed cardioembolic by the local study physician were excluded.[4]

At enrollment, subjects underwent a baseline history, physical and neurologic examinations including the National Institute of Health Stroke Scale (NIHSS), and laboratory analysis including casual plasma glucose and lipid panel. NIHSS was subsequently determined at 12 weeks, 6, 12, 16, and 24 months, termination, and any visit prior to medication rechallenge. For longitudinal analysis, blood pressure measurements from follow-up examinations at baseline and 6, 10, 12, 16, 20, and 24 months and laboratory analyses at baseline and 12 and 24 months were used. The local site investigators assigned eligibility and recurrent stroke subtype according to the Trial of ORG 10172 in Acute Stroke Treatment (TOAST) criteria and completed the modified Barthel Index (BI), a 20-point measure of activities of daily living, and the Glasgow Outcome Score (GOS), a measure of disability (1 = death,

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2 = persistently vegetative, 3 = severely disabled, 4 = moderately disabled, and 5 = good recovery), for each subject at baseline, 6 months, and termination.[5] For those experiencing a recurrent stroke during follow-up, NIHSS, BI, and GOS were determined by trained local site investigative personnel at the termination visit and compared to baseline. Recurrent strokes were verified and systematically assigned a possible or probable stroke subtype by a central adjudication committee based on available source documentation.[4]

Subjects were defined as hypertensive if they reported a history of hypertension (HTN) or use of blood pressure–lowering agents or had a baseline blood pressure measurement ≥140/90 mm Hg.[6] The protocol specified that blood pressure be taken after the patient was seated for 5 minutes at least 30 minutes after the ingestion of caffeine or smoking. The average of two measurements in the right arm at least 2 minutes apart was to be recorded and further measurements taken if the initial difference was >5 mm Hg. Only blood pressure measurements taken on study prior to adjudication-supplied date of stroke recurrence were used for analysis. As recurrent stroke may have adversely affected blood pressure, blood pressure measurements taken at the time of termination due to stroke were not used in analysis.

Subjects were defined as having diabetes mellitus (DM) if they reported a history of DM or use of insulin or oral hypoglycemic agents or had a baseline casual plasma glucose measurement ≥200 mg/dL.[7] Subjects were defined as having dyslipidemia (DL) if they reported a history of hypercholesterolemia, use of lipid-lowering agents, total cholesterol measurement ≥240 mg/dL, or high-density lipoprotein measurement <35 mg/dL.[8] Body mass index (BMI) was calculated using the subject's weight in kilograms divided by the square of the height in meters. BMI was classified as underweight (<18.5 kg/m^2), normal (18.5 to 24.9 kg/m^2), overweight (25 to 29.9 kg/m^2), class 1 obesity (30 to 34.9 kg/m^2), class 2 obesity (35 to 39.9 kg/m^2), or class 3 obesity (≥40 kg/m^2).[9]

History of stroke, myocardial infarction, cardiac surgery, peripheral arterial surgery, leg claudication, smoking, hormone use, and regular leisure exercise were ascertained by self-report. The presence of coronary artery disease was defined as a reported history of myocardial infarction or cardiac surgery and peripheral vascular disease defined as a reported history of peripheral arterial surgery or leg claudication.

Statistical analysis. All analyses were conducted using SAS (SAS Institute Inc., Cary, NC) statistical software and compared subjects with recurrent fatal and nonfatal stroke to subjects without. All data collected from randomized subjects were used for this analysis with the exception of physiologic covariate data collected on or after adjudication-supplied date of stroke recurrence. Categorical values were compared using χ^2 tests and Fisher exact test. Continuous values were compared using Wilcoxon and t tests. Univariate analyses were performed using Cox proportional hazards modeling to obtain hazard estimates with respect to key covariates. Longitudinal analysis of key covariates was performed using Cox proportional hazards modeling with individual time-dependent covariates. Multivariate analyses consisted of Cox proportional hazards modeling with a combination of fixed (those assessed at baseline) and time-varying covariates. Backward elimination techniques (with $p < 0.10$ for a covariate to remain in the model) were used in multivariate analyses to assess the relative influence of baseline covariates such as history of HTN, history of DM, history of DL, age, gender, and time-varying covariates such as NIHSS score, BI, GOS score, blood pressure, glucose and cholesterol levels, and treatment group. Significance of resulting hazard estimates were reflected by 95% CIs and relevant p values. After significant covariates were identified, models that included clinically meaningful interactions between these covariates were also assessed.

Results. *Baseline characteristics.* The baseline characteristics of the 1,809 subjects enrolled in the AAASPS are shown in table 1. The eligibility stroke subtypes were small vessel occlusive, 67.5%; large vessel atherothrombotic, 19.7%; and other/unknown, 12.5%. There were 191 (10.6%) recurrent strokes during the follow-up period. The mean interval between eligibility stroke and recurrent stroke was 325 days (median 287 days, SD = 224 days).

Table 1 *Baseline characteristics*

Age, y	
Mean ± SD	61.3 ± 10.6
Median (range)	61 (28–89)
Female, %	53.4
NIHSS	
Mean ± SD	2.8 ± 2.6
Median (range)	2 (0–18)
BI	
Mean ± SD	19 ± 2.5
Median (range)	20 (3–20)
GOS, %	
No/minimal disability	63.0
Moderate disability	32.0
Severe disability	4.9
Eligibility stroke subtype, %	
Large vessel atherothrombotic	19.7
Small vessel occlusive	67.5
Other/unknown	12.8
Factor, %	
Hypertension	93.3
Diabetes mellitus	42.4
Dyslipidemia	60.8
Obesity (BMI >30 kg/m^2)	41.8
Multiple prior strokes	23.2
Myocardial infarction	9.4
Cardiac surgery	3.8
Peripheral arterial vascular surgery	1.7
Current cigarette smoking, %	38.2
Regular exercise, %	38.7
Family history, %	
Stroke	42.0
Myocardial infarction	33.7

NIHSS = National Institute of Health Stroke Scale, BI = Barthel Index, GOS = Glasgow Outcome Scale; BMI = body mass index.

Only 39.0% of recurrent strokes were considered to be possible or probable small vessel occlusive subtype, 16.1% to be large vessel atherothrombotic subtype, and 36.8% were other or of unknown ischemic etiology. (table 2) Nine (4.7%) recurrent strokes were hemorrhagic including one subarachnoid hemorrhage. Recurrent stroke subtype was different than eligibility stroke subtype in 57% of cases.

Disability and recurrent stroke. Stroke recurrence resulted in an average 1.5-point increase in the NIHSS (range −4 to 30; SD = 5.4; $p < 0.001$) and a 3.5-point decrease in BI (range −20.0 to 4.0; SD = 5.6; $p < 0.001$) compared to baseline representing worsening neurologic impairment and functional status. Of the 191 recurrent strokes, 102 (53%) were considered nondisabled by the eligibility stroke according to the baseline GOS. However, 49 of these 102 subjects (48%) were disabled at the termination visit or died after stroke recurrence ($p < 0.0001$).

Table 2 *Recurrent stroke subtypes (n = 191)*

Subtype	Frequency (%)
Large vessel atherothrombotic	
Possible	17 (8.8)
Probable	14 (7.3)
Cardioembolic	
Possible	3 (1.6)
Probable	2 (1.0)
Small vessel (lacunar)	
Possible	35 (18.0)
Probable	40 (21.0)
Other/unknown ischemic etiology	71 (36.8)
Parenchymatous hemorrhage	7 (3.6)
Subarachnoid hemorrhage	1 (0.5)
Hemorrhagic infarction	1 (0.5)

Predictors and factors associated with stroke recurrence. In univariate analysis, DM (hazard ratio [HR] 1.470, 95% CI: 1.108 to 1.949, $p = 0.008$), history of multiple strokes (HR 1.417, 95% CI: 1.055 to 1.904, $p = 0.021$), and disability (GOS <5) (HR 1.452, 95% CI: 1.093 to 1.928, $p = 0.010$) were all found to be associated with recurrent stroke risk. In addition, a trend was seen for HTN (HR 2.014, 95% CI: 0.947 to 4.284, $p = 0.069$). Table 3 reflects univariate analyses, i.e., in the case of each covariate listed, Cox regression was performed with that covariate as the only independent variable. The p value indicates the significance of the covariate with respect to that univariate model.

Table 3 *Univariate Cox regression analyses of baseline predictors of recurrent stroke*

Factor	Hazard ratio	95% CI	p Value
Hypertension	2.014	0.947–4.284	0.069
Diabetes mellitus	1.470	1.108–1.949	0.008
Dyslipidemia	0.934	0.701–1.245	0.641
Metabolic syndrome	1.105	0.731–1.671	0.635
Regular leisure exercise	1.006	0.754–1.343	0.965
Coronary artery disease	1.253	0.902–1.741	0.178
Peripheral vascular disease	1.095	0.636–1.886	0.744
Multiple strokes	1.417	1.055–1.904	0.021
Age	1.004	0.991–1.018	0.544
Hormone replacement therapy	1.025	0.605–1.736	0.926
Disability	1.452	1.093–1.928	0.010
Current vs never smoker	1.134	0.816–1.576	0.454
BMI ≥30 vs normal BMI	0.963	0.668–1.390	0.842
Large vessel subtype	1.094	0.775–1.544	0.611
Small vessel subtype	0.948	0.703–1.277	0.724
Family history of stroke	1.071	0.806–1.423	0.636
Family history of MI	0.860	0.634–1.166	0.331

BMI = body mass index; MI = myocardial infarction.

Table 4 *Longitudinal analysis* of dynamic risk factors as predictors of recurrent stroke*

Factor	Hazard ratio	95% CI	p Value
Glucose	1.010	0.990–1.030	0.320
Total cholesterol	0.991	0.960–1.023	0.584
Systolic blood pressure†	1.103	1.031–1.179	0.004
Diastolic blood pressure†	1.041	0.913–1.187	0.546
Pulse pressure†	1.123	1.041–1.213	0.003
Mean arterial pressure†	1.123	1.001–1.260	0.048

*Repeated-measures analysis.
†Per 10-mm Hg increase.

Longitudinal analysis resulted in a hazard for recurrent stroke for each 10 mm Hg increase in systolic BP of 1.103 (95% CI: 1.031 to 1.179, $p = 0.004$), pulse pressure 1.123 (95% CI: 1.041 to 1.213, $p = 0.003$), and mean arterial pressure 1.123 (95% CI: 1.001 to 1.260, $p = 0.048$). There was no increase in the hazard for recurrent stroke for increase in serum glucose level (HR 1.010, 95% CI: 0.990 to 1.030, $p = 0.320$), total cholesterol level (HR 0.991, 95% CI: 0.960 to 1.023, $p = 0.584$), or diastolic BP (HR 1.041, 95% CI: 0.913 to 1.187, $p = 0.546$) (table 4).

Multivariate analysis revealed increases in the recurrent stroke hazard for increases in GOS (HR 1.449, 95% CI: 1.071 to 1.961, $p = 0.016$) and increases in longitudinal pulse pressure (HR 1.009, 95% CI: 1.001 to 1.017, $p = 0.029$). A trend was seen for history of multiple strokes (HR 1.365, 95% CI: 0.986 to 1.889, $p = 0.061$) and DM (HR 1.340, 95% CI: 0.993 to 1.809, $p = 0.056$) (table 5).

In the final Cox regression model, both the likelihood and score tests indicated a reasonably significant fit ($p < 0.003$). Additionally, we performed stepwise logistic regression using stroke recurrence as the dependent variable using the same covariates. Lastly, time-to-event analyses using the log rank statistic were performed to compare stroke recurrence between those with a given characteristic at baseline (HTN, DM, DL, disabled, obesity, metabolic syndrome, multiple previous strokes, smoking, lack of exercise, coronary artery disease, or peripheral vascular disease) and those without. These three very different analyses led to the same conclusion, that HTN, disability, DM, and multiple previous strokes were significant predictors of stroke recurrence. Yet, the models also indicated that there are influences of stroke risk that are not explained by these covariates alone.

Table 5 *Multivariate analysis* for predictors of recurrent stroke*

Factor	Hazard ratio	95% CI	p Value
Multiple strokes	1.365	0.986–1.889	0.061
Diabetes mellitus	1.340	0.993–1.809	0.056
Pulse pressure†	1.009	1.001–1.017	0.029
Disability	1.449	1.071–1.961	0.016

*Via Cox proportional hazards stepwise regression analysis.
†Longitudinal pulse pressure over time.

Discussion. African Americans have been underrepresented in clinical trials, and data regarding stroke recurrence are lacking. Although those who suffered cardioembolic stroke required endarterectomy or were too severely disabled to participate in regular follow-up were excluded, the AAASPS provides our first opportunity to systematically examine the characteristics of stroke recurrence and impact of vascular risk factors on stroke recurrence in a large number of African American stroke survivors.

In our population, recurrent stroke lead to disability at the termination visit or death (GOS <5) in 48% of patients whose eligibility stroke resulted in good outcome at baseline as evidenced by a poorer overall neurologic function and ability to perform activities of daily living by NIHSS and BI. Although these data do not indicate whether African Americans are more likely to experience more disability than, for example, white Americans, the results support a high likelihood of disability or death in African American ischemic stroke survivors who experience stroke recurrence. These findings further underscore the importance of recurrent stroke prevention measures.

Several risk factors affected stroke recurrence. Longitudinal pulse pressure was a multivariate predictor of recurrence in this cohort. In fact, there was a 12% linear increase in the hazard of recurrent stroke for every 10-mm Hg increase in the pulse pressure with repeated-measures analysis. Similar longitudinal results were seen for systolic and mean arterial blood pressure levels. The impact of blood pressure on stroke recurrence is particularly important given recent clinical trial data supporting the beneficial effects of blood pressure lowering on recurrent stroke risk.[10]

Disability prior to stroke recurrence was another predictor of stroke recurrence. We suspect that its impact may be underrepresented in our data because the protocol excluded those with disability too severe to attend regular follow-up. However, these individuals would likely have difficulty accessing medical care, resulting in poor risk factor control leading to higher stroke recurrence risk.

A trend was seen for history of multiple strokes as a predictor of stroke recurrence, further supporting the notion that "stroke begets stroke."[11] This also suggests a possible magnification of the recurrent stroke risk above that of a single previous stroke as all participants in the AAASPS had a history of at least one stroke at the time of enrollment. This finding was independent of baseline level of disability. Furthermore, a single stroke prior to the eligibility stroke was reported most commonly in those with multiple previous strokes and only <5% of both overall subjects and those with recurrent stroke during follow-up had a history of greater than one stroke prior to the eligibility stroke, which limited statistical power to detect any additional relationship between increasing stroke burden and increasing recurrent stroke risk.

History of DM was highly predictive of recurrent stroke in univariate analysis but did not reach significance in multivariate analysis. Furthermore, longitudinal control of glucose had no impact on stroke recurrence. Despite the known benefits of glycemic control in reducing microvascular complications such as diabetic retinopathy, nephropathy, and neuropathy and the higher stroke morbidity and mortality associated with elevated serum glucose at onset of cerebral ischemia,[12,13] our results suggest additional factors associated with DM or its treatment beyond serum glucose control that contribute to recurrent cerebrovascular disease.

No association between a history of DL or measured serum cholesterol level and recurrent stroke risk was seen. However, we excluded subjects with symptomatic extracranial internal carotid artery stenosis requiring endarterectomy for which there may be a greater impact of serum lipids. In addition, there was increasing use of statin medications and overall mean reductions in lipid levels over the course of the study that may have obscured the relationship between lipids and recurrent stroke risk. Furthermore, other non–lipid-lowering beneficial mechanisms of the statins have been proposed[14] that may also have contributed to our results.

We have previously shown an association between increasing BMI and higher risk factor burden as well as higher baseline blood pressure level in the AAASPS.[15] However, obesity was not shown to be an independent predictor of stroke recurrence.

Our study has several limitations. The systematic exclusion of subjects with extracranial internal carotid artery stenosis and cardioembolic eligibility strokes per the AAASPS protocol limits generalizing our findings to African Americans with these stroke subtypes. Additionally, the acute phase of stroke can transiently elevate blood pressure and serum glucose levels and normalize lipids. This could result in an overestimation of the frequency of diagnosis of HTN and DM and underestimation of the frequency of DL. However, subjects were enrolled a mean of 45 days from the eligibility stroke (only 15% within 7 to 14 days) and repeated-measures analysis would have further minimized these potential acute phase effects. Therefore, this effect seems unlikely to have affected our data. Using casual plasma glucose rather than fasting or oral glucose tolerance tests may also have resulted in an underestimation of the diagnosis of DM at baseline. Similarly, nonfasting lipid levels may have led to overestimation of the diagnosis of DL at baseline. However, it is unlikely that nonfasting glucose and lipid levels would have significantly obscured an association with recurrent stroke on repeated-measures analysis.

Furthermore, the AAASPS protocol did not require systematic evaluation for recurrent stroke by the treating physicians. Although recurrent stroke events were adjudicated by an expert panel, 37% were assigned a category of "other" or "unknown" etiology. Considering the lack of uniform diagnostic

recurrent stroke workup and the TOAST criteria limitations, this could have affected adversely on classification of recurrent stroke subtype. Last, termination due to stroke examinations were performed a mean of 38 days (39% within 2 weeks) from stroke recurrence, which may have been early enough in the stroke recovery phase for many subjects to potentially improve beyond termination resulting in actual lower long-term disability than that quantified on this examination.

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